



## Clinical trial results:

### A Prospective, randomized, single blind, multicenter Phase III study of organ perfusion with Custodiol-N solution compared with Custodiol solution in Heart transplantation

#### Summary

EudraCT number	2012-001112-29
Trial protocol	DE AT
Global end of trial date	02 September 2020

#### Results information

Result version number	v1 (current)
This version publication date	28 April 2022
First version publication date	28 April 2022

#### Trial information

##### Trial identification

Sponsor protocol code	CL-N-HTX-CSM-III/04/12
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02869022
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Dr. Franz Köhler Chemie GmbH
Sponsor organisation address	Werner-von – Siemens-Str. 14-28, Bensheim, Germany, 64625
Public contact	Dr. Roman Petrov, Dr. Franz Köhler Chemie GmbH, +49 625110830, r.petrov@koehler-chemie.de
Scientific contact	Dr. Roman Petrov, Dr. Franz Köhler Chemie GmbH, +49 625110830, r.petrov@koehler-chemie.de

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 September 2020
Global end of trial reached?	Yes
Global end of trial date	02 September 2020
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The objective of this investigation is to demonstrate non-inferiority in outcome of Custodiol-N against Custodiol in heart transplantation.

CK-MB peak value from 4 to 168 hours after release of the aortic cross clamp (day 1: measurements 4, 8, 12, 16, 20, 24 hours  $\pm$  30 min; day 2-3: measurements 8, 16 and 24 hours  $\pm$  2 hours; day 4-7 one time/day).

Protection of trial subjects:

Adverse events were documented systematically.

Background therapy: -

Evidence for comparator:

Custodiol is in use in many cardiac centres throughout the world for the indication heart transplantation.

Actual start date of recruitment	01 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 60
Country: Number of subjects enrolled	Germany: 45
Worldwide total number of subjects	105
EEA total number of subjects	105

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	104

From 65 to 84 years	1
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study population was recruited patients on the waiting list for heart transplantation.

### Pre-assignment

Screening details:

Patients (organ recipients) were screened for inclusion and exclusion criteria.

### Period 1

Period 1 title	Therapy (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Custodiol ®
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Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Custodiol ®
Investigational medicinal product code	B05XA16
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

The perfusion of the donor heart with 2° - 8° C cold Custodiol-N / Custodiol ® was performed for a minimum of 7 minutes. After mobilisation and appropriate preparation of heart and blood vessels and clamping of the aorta, perfusion with 4 litres of Custodiol-N / Custodiol ® was started via aorta. In case of donor lung explantation, separate perfusion of the lungs was ensured to avoid the perfusion of the lungs with the study medication.

<b>Arm title</b>	Custodiol-N
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Custodiol-N
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

The perfusion of the donor heart with 2° - 8° C cold Custodiol-N / Custodiol ® was performed for a minimum of 7 minutes. After mobilisation and appropriate preparation of heart and blood vessels and clamping of the aorta, perfusion with 4 litres of Custodiol-N / Custodiol ® was started via aorta. In case of donor lung explantation, separate perfusion of the lungs was ensured to avoid the perfusion of the lungs with the study medication.

<b>Number of subjects in period 1</b>	Custodiol ®	Custodiol-N
Started	52	53
Completed	52	52
Not completed	0	1
Adverse event, serious fatal	-	1

## Baseline characteristics

## End points

### End points reporting groups

Reporting group title	Custodiol ®
Reporting group description: -	
Reporting group title	Custodiol-N
Reporting group description: -	

### Primary: CK-MB peak value (FAS)

End point title	CK-MB peak value (FAS)
End point description:	
Full analysis set	
End point type	Primary
End point timeframe:	
4 to 168 hours after release of the aortic cross clamp (day 1: measurements 4, 8, 12, 16, 20, 24 hours $\pm$ 30 min; day 2-3: measurements 8, 16 and 24 hours $\pm$ 2 hours; day 4-7 one time/day)	

End point values	Custodiol ®	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: U/L				
arithmetic mean (standard deviation)	176.94 ( $\pm$ 189.61)	130.51 ( $\pm$ 69.60)		

### Statistical analyses

Statistical analysis title	CK-MB peak value (FAS)
Comparison groups	Custodiol ® v Custodiol-N
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 <sup>[1]</sup>
Method	log-linear

Notes:

[1] - Noninferiority of Custodiol-N by 30%.

Overall treatment effect in the FAS was 0.764 (95% confidence interval of a treatment effect [0.672; 0.931]).

### Primary: CK-MB peak value (PP)

End point title	CK-MB peak value (PP)
End point description:	
End point type	
End point type	Primary

End point timeframe:

4 to 168 hours after release of the aortic cross clamp (day 1: measurements 4, 8, 12, 16, 20, 24 hours  $\pm$  30 min; day 2-3: measurements 8, 16 and 24 hours  $\pm$  2 hours; day 4-7 one time/day)

End point values	Custodiol ®	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	41		
Units: U/L				
arithmetic mean (standard deviation)	178.17 ( $\pm$ 202.41)	136.29 ( $\pm$ 70.72)		

### Statistical analyses

Statistical analysis title	CK-MB peak value
Statistical analysis description: CK-MB peak value within 168 h from opening of aortic cross clamp	
Comparison groups	Custodiol ® v Custodiol-N
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001 [2]
Method	log-linear model

Notes:

[2] - 1-sided p-value for noninferiority to 30 per cent

### Secondary: Catecholamine requirement, defined as "yes" or "no"

End point title	Catecholamine requirement, defined as "yes" or "no"
End point description:	
End point type	Secondary
End point timeframe: 4 - 168 h after opening of aortic cross clamp	

End point values	Custodiol ®	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Patients				
Catecholamins 'yes'	52	53		
Catecholamins 'no'	0	0		



## Statistical analyses

No statistical analyses for this end point

### Secondary: Patient survival at 7 days and 1, 3 and 12 months

End point title	Patient survival at 7 days and 1, 3 and 12 months
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End point description:

End point type	Secondary
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End point timeframe:

at 7 days and 1, 3 and 12 months from surgery

End point values	Custodiol ®	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Patients				
7 days	51	53		
1 month	51	53		
3 months	50	53		
12 months	47	47		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Complications

End point title	Complications
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End point description:

Retransplantation was reported under the endpoint 'primary poor function', procedural complications were reported under 'adverse events'.

End point type	Secondary
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End point timeframe:

From transplantation to day 7 after surgery

End point values	Custodiol ®	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Patients with complications	42	39		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Length of ICU stay

End point title	Length of ICU stay
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End point description:

Duration in days as difference between end and start date.

End point type	Secondary
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End point timeframe:

After surgery until end of ICU stay

End point values	Custodiol ®	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	52		
Units: days				
median (inter-quartile range (Q1-Q3))	10.0 (6 to 19)	8.0 (5 to 11.5)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Requirement of IABP

End point title	Requirement of IABP
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End point description:

End point type	Secondary
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End point timeframe:

From end of surgery to day 7 after surgery

End point values	Custodiol ®	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Patients	5	3		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Ejection fraction

End point title	Ejection fraction
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End point description:

End point type	Secondary
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End point timeframe:

Day 1 and day 7 after transplantation

End point values	Custodiol ®	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41 <sup>[3]</sup>	41 <sup>[4]</sup>		
Units: percent volume/volume				
arithmetic mean (standard deviation)				
Day 1	52.61 (± 11.82)	55.40 (± 11.19)		
Day 7	53.76 (± 14.46)	53.71 (± 9.85)		

Notes:

[3] - day 1 n=41

day7 n=38

[4] - day 1 n=40

day 7 n=41

### Statistical analyses

No statistical analyses for this end point

### Secondary: Cardiac index

End point title	Cardiac index
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End point description:

End point type	Secondary
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End point timeframe:

6h/12h/18h/24h after opening of the aortic cross clamp

End point values	Custodiol ®	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34 <sup>[5]</sup>	40 <sup>[6]</sup>		
Units: liter/min/m <sup>2</sup>				
arithmetic mean (standard deviation)				
6h	2.70 (± 0.73)	3.11 (± 1.01)		
12h	2.61 (± 0.84)	3.27 (± 0.82)		
18h	2.69 (± 0.76)	3.16 (± 0.85)		
24h	2.87 (± 0.77)	3.05 (± 0.74)		

Notes:

[5] - 6h n=26

12h n=28

18h n=33

24h n=34

[6] - 6h n=32  
12h n=39  
18h n=38  
24h n=40

## Statistical analyses

No statistical analyses for this end point

## Secondary: Enddiastolic ventricle volumes

End point title	Enddiastolic ventricle volumes
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End point description:

End point type	Secondary
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End point timeframe:

Day 1 and day 7 after transplantation

End point values	Custodiol ®	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30 <sup>[7]</sup>	29 <sup>[8]</sup>		
Units: mL				
arithmetic mean (standard deviation)				
Day 1	78.10 (± 39.93)	81.21 (± 29.75)		
Day 7	82.15 (± 37.88)	92.74 (± 31.57)		

Notes:

[7] - Number of subjects:

Day 1 n = 30,

day 7 n = 27

[8] - Number of subjects:

Day 1 n=29

Day 7 n= 27

## Statistical analyses

No statistical analyses for this end point

## Secondary: Endsystolic ventricle volumes

End point title	Endsystolic ventricle volumes
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End point description:

End point type	Secondary
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End point timeframe:

Day 1 and day 7 after transplantation

End point values	Custodiol ®	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	30		
Units: mL				
arithmetic mean (standard deviation)				
Day 1	37.27 (± 18.93)	38.79 (± 19.86)		
Day 7	40.15 (± 23.40)	43.56 (± 17.07)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Primary poor function

End point title	Primary poor function
End point description: Need for assist device and retransplantation	
End point type	Secondary
End point timeframe: Until day 7 after transplantation	

End point values	Custodiol ®	Custodiol-N		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: Patients with primary poor function				
Need for assist device retransplantation	11 0	5 1		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From transplantation to day 7

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	22
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### Reporting groups

Reporting group title	Custodiol® safety data set
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Reporting group description: -

Reporting group title	Custodiol-N safety data set
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Reporting group description: -

Serious adverse events	Custodiol® safety data set	Custodiol-N safety data set	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 52 (40.38%)	15 / 53 (28.30%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Investigations			
Investigations			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	7 / 52 (13.46%)	5 / 53 (9.43%)	
occurrences causally related to treatment / all	0 / 8	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	5 / 52 (9.62%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	1 / 5	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac disorders			
Cardiac disorders			

subjects affected / exposed	4 / 52 (7.69%)	8 / 53 (15.09%)	
occurrences causally related to treatment / all	0 / 6	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	4 / 52 (7.69%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Immune system disorders			
subjects affected / exposed	1 / 52 (1.92%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	5 / 52 (9.62%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	1 / 52 (1.92%)	5 / 53 (9.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and infestations			
subjects affected / exposed	2 / 52 (3.85%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	Custodiol® safety data set	Custodiol-N safety data set	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 52 (88.46%)	46 / 53 (86.79%)	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	8 / 52 (15.38%)	3 / 53 (5.66%)	
occurrences (all)	8	3	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	5 / 52 (9.62%)	8 / 53 (15.09%)	
occurrences (all)	7	11	
Blood and lymphatic system disorders			
Blood and lymphatic disorders			
subjects affected / exposed	15 / 52 (28.85%)	18 / 53 (33.96%)	
occurrences (all)	24	23	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	7 / 52 (13.46%)	9 / 53 (16.98%)	
occurrences (all)	7	10	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	12 / 52 (23.08%)	12 / 53 (22.64%)	
occurrences (all)	12	12	
Infections and infestations			
Infections and infestations			
subjects affected / exposed	11 / 52 (21.15%)	7 / 53 (13.21%)	
occurrences (all)	11	7	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	2 / 52 (3.85%)	5 / 53 (9.43%)	
occurrences (all)	2	7	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 February 2019	Patient number increased from 90 to 105

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported